PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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in its capacity as elected Office

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International filing date (day/month/year) 25 May 2000 (25.05.00)	**Priority date** (day/month/year) 25 May 1999 (25.05.99)
Applicant KUMAR, Naresh et al	

1. The designated Office is hereby notified of its election made:

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27 November 2000 (27.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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PATENT COOPERATI I TREATY

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NOTIFICATION CONCERNING
AMENDMENTS OF THE CLAIMS

(PCT Rule 62 and
Administrative Instructions, Section 417)

To:

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18 January 2001 (18.01.01)	
International application No.	International filing date (day/month/year)
PCT/IB00/00708	25 May 2000 (25.05.00)

Applicant

RANBAXY LABORATORIES LIMITED et al

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417).

The International Bureau of WIPO
34, chemin des Colombettes
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WO 00/71124 A1

(54) Title: AMORPHOUS FORM OF FEXOFENADINE HYDROCHLORIDE

(57) Abstract: This invention relates to an amorphous form of fexofenadine hydrochloride, to a process for the preparation thereof, and to a composition containing it.

WE CLAIM :

1. Fexofenadine hydrochloride in an amorphous form.

2. A pharmaceutical composition containing a therapeutically effective amount of the amorphous form of claim 1 together with one or more pharmaceutical carriers or excipients.

3. A process for the preparation of fexofenadine hydrochloride in an amorphous form which comprises dissolving crystalline fexofenadine hydrochloride in a suitable solvent or dissolving fexofenadine base in a suitable solvent and adding a suitable solvent containing hydrogen chloride and recovering fexofenadine hydrochloride from said solution by spray drying or freeze drying technique.

4. The process of claim 3, wherein suitable solvent is selected from the group consisting of lower alkanol, ester, ketone, chlorinated solvent and mixtures thereof.

5. The process of claim 4, wherein lower alkanol includes primary, secondary and tertiary alcohols having from one to six carbon atoms.

6. The process of claim 5, wherein said lower alkanol is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol or n-butanol and mixtures thereof.

7. The process of claim 6, wherein the solvent is methanol, ethanol or isopropanol.

8. The process of claim 4, wherein the ester solvent is selected from ethyl acetate or n-butyl acetate.

9. The process of claim 4, wherein the ketone solvent is acetone, methylethyl ketone, 2-butanone, 4-methylpentan-2-one.

10. The process of claim 4, wherein the chlorinated solvent is chloroform, dichloromethane or carbontetrachloride.

11. The process of claim 3, wherein fexofenadine hydrochloride in an amorphous form is isolated from said solution by spray drying.

12. The process of claim 3, wherein the spray drying is effected in the presence of an inert gas.

13. The process of claim 3, wherein fexofenadine hydrochloride in an amorphous form is isolated from said solution by freeze drying.

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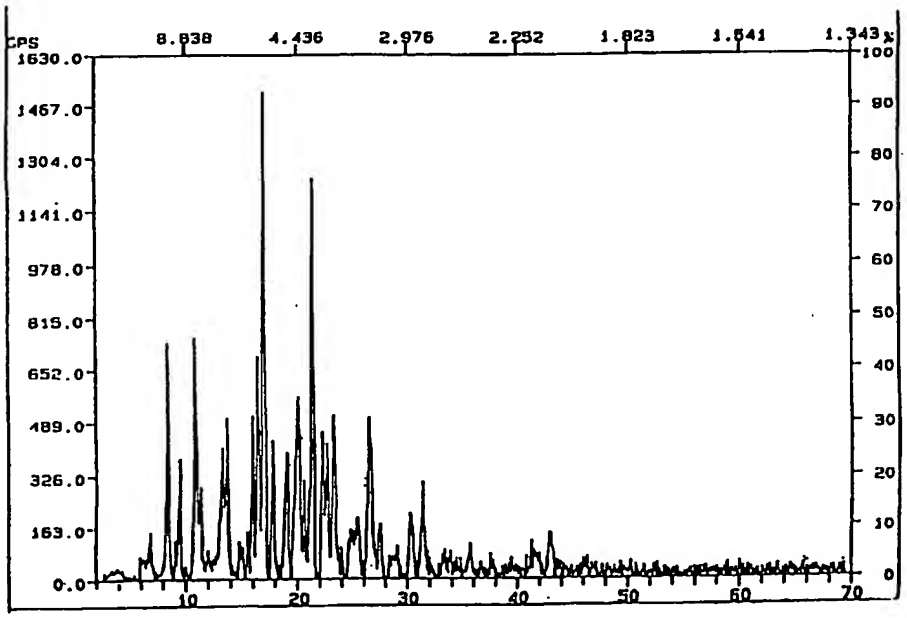
(54) Title: CRYSTAL MODIFICATION



(57) Abstract: A novel crystal form of, α-dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]benzeneacetic acid hydrochloride, processes for its preparation and its pharmaceutical use are disclosed.

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Crystal Modification

Summary

This invention relates to a novel crystal form of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride, a process for its preparation and pharmaceutical formulations thereof.

Background

The compound α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride has been named according to the U.S.A.N. as fexofenadine hydrochloride ("F-HCl"). It is known as the active metabolite of the non-sedating antihistamine terfinadine and is itself marketed in the United States as a non-sedating antihistamine. F-HCl and its preparation are described, for example, in U.S Patent No. 5,578,610, which is here incorporated by reference. Anhydrous and hydrated crystal forms of F-HCl identified as Forms I, II, III and IV are described in WO 95/31437.

The present invention relates to a novel F-HCl crystal modification, hereinafter designated as Form A, which is distinguished from previously known crystal forms by physical and spectroscopic properties such as melting point, x-ray powder diffraction pattern, solid state NMR spectrum and infrared spectrum. The Form A crystal modification of F-HCl is prepared in an advantageously environmentally friendly manner.

Brief Description of the Drawings

Figure 1 shows the powder x-ray diffraction pattern of the Form A crystal modification of F-HCl (λ=1.540600).

Figure 2 shows the solid state Carbon-13 NMR of the Form A crystal modification of F-HCl over the chemical shift range of 275 to –100 ppm.

Figure 3 shows the FTIR spectrum of the Form A crystal modification of F-HCl as a mull with Nujol oil.

Figure 4 shows the FTIR spectrum of Nujol oil.

Detailed Description

The Form A crystal modification of F-HCl is characterized by its physical and spectroscopic properties which are described in detail below.

The Form A crystal modification of F-HCl has a characteristic melting point in the range from about 138°C to 148°C, more specifically about 142°C to about 145°C.

Figure 1 is the powder x-ray diffraction pattern of the Form A crystal modification of F-HCl. The powder x-ray diffraction pattern of Form A is characterized by peaks at about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35 d-spacing units. The x-ray diffraction pattern depicted in Figure 1 is summarized in Table 1:

Table 1 – Powder X-Ray Diffraction Peaks for the Form A crystal modification of F-HCl

Peak No.	°2θ[1]	d-space[1]	RELATIVE INTENSITY[2]	Peak No.	°2θ[1]	d-space[1]	RELATIVE INTENSITY[2]
1	5.99	14.74	4	23	21.38	4.15	82
2	6.59	13.40	4	24	22.27	3.98	28
3	6.83	12.91	9	25	22.68	3.91	27
4	8.42	10.49	45	26	23.29	3.81	33
5	9.09	9.71	7	27	24.82	3.53	9
6	9.47	9.32	23	28	25.03	3.55	9
7	10.85	8.14	48	29	25.45	3.49	12
8	11.29	7.83	18	30	26.55	3.35	33
9	11.97	7.39	5	31	27.50	3.24	11
10	12.45	7.09	4	32	29.09	3.06	6
11	13.26	6.66	26	33	30.31	2.94	13
12	13.67	6.46	31	34	31.40	2.34	17
13	14.80	5.93	7	35	31.82	2.81	5
14	15.08	5.86	6	36	33.34	2.68	5
15	15.54	5.69	9	37	35.66	2.51	5
16	15.97	5.54	31	38	35.78	2.50	5
17	16.46	5.37	44	39	41.29	2.13	6
18	17.02	5.29	100	40	41.55	2.17	5
19	17.80	4.97	27	41	41.73	2.16	5
20	19.01	4.65	26	42	42.90	2.13	9
21	20.05	4.42	36	43	43.09	2.09	9
22	20.57	4.31	19				

1 – peak values reported in Table 1 are truncated to 2 decimal places from the instrument report and reported without regard to significant figures

2 – intensities may vary significantly due to orientation effects

Variances in the d-spacing values reported for any x-ray diffraction peak within ± 1% are considered insignificant. The use of the expression "about" when describing the position of an powder x-ray diffraction peak is intended to provide a basis for including such insignificant variances within the characterization of the Form A crystal modification.

Figure 2 shows the carbon-13 NMR spectrum of the Form A crystal modification of F-HCl measured using 600 transients and a 6 second pulse delay over the chemical shift range of 275 to –100 ppm. Characteristic signals are observed at chemical shifts of 187.4, 180.3, 74.5, 48.8, and 29.8 ppm. Table 2 summarizes the signals observed in the solid state carbon-13 NMR of the Form A crystal modification of F-HCl.

Table 2 – Solid State NMR Signals of The Form A crystal modification of F-HCl

peak #	p.p.m.	peak #	p.p.m.
1	187.4	12	53.9
2	180.3	13	48.8*
3	148.3	14	43.2
4	145.6	15	40.2
5	142.0	16	36.5
6	130.4*	17	32.9
7	128.2*	18	29.8
8	126.4*	19	26.0*
9	78.9*	20	24.6*
10	74.5	21	22.6
11	57.5		

* denotes most intense signals

The chemical shifts reported for solid state carbon-13 NMR signals can vary from sample to sample by up to 1 ppm. The use of the expression "about" to describe the chemical shift of an NMR signal is intended to include such variances within the characterization of the Form A crystal modification.

One or more of the physical properties and/or spectroscopic properties are the basis for characterizing the Form A crystal modification of F-HCl.

For example, the Form A crystal modification of F-HCl is properly described as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from 138°C to 148°C, or as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from about 142°C to about 145°C. It is also properly described as crystalline α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having powder x-ray diffraction peaks at d spacings of 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35 or the x-ray diffraction pattern depicted in Table 1. It is also properly described as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having solid state carbon-13 NMR signals at chemical shifts of 187.4, 180.3, 74.5, 48.8, and 29.8 ppm, or as having the solid state carbon-13 NMR spectrum depicted in Figure 2 and Table 2. It is also properly described as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having the Fourier Transform Infrared Spectrum depicted in Figure 3A as a Nujol oil mull.

The Form A crystal modification is also properly described by a combination of physical and/or spectroscopic properties.

Thus, Form A F-HCl is a substantially pure crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by powder x-ray diffraction peaks at d spacings of about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35 and a melting point in the range from about 142°C to about 145°C.

Form A F-HCl is also a crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by solid state carbon-13 NMR signals at chemical shifts of about 187.4, 180.3, 74.5, 48.8, and 29.8 ppm and powder x-ray diffraction peaks at d spacings of

about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35. It is also such a crystal modification having a melting point in the range from about 142°C to about 145°C in pure form.

Form A F-HCl is also properly described as a crystal modification having the solid state carbon-13 NMR spectrum depicted in Figure 2 and the x-ray powder diffraction pattern depicted in Figure 1. It is also such a crystal modification having the Fourier Transform Infrared Spectrum depicted in Figure 3A as a Nujol oil mull and can be further characterized as having a melting point in the range from 138°C to 148°C in substantially pure form, preferably from about 142°C to about 145°C in pure form.

Preferably, the Form A crystal modification of F-HCl is in substantially pure form - substantially pure form being intended to mean that at least 80 percent by weight of the crystalline F-HCl in the sample is present as Form A. Most preferably, the Form A crystal modification is in pure form meaning that at least 90% of the crystalline F-HCl in the sample is present as Form A. The present invention also relates to highly pure Form A crystal modification meaning that the material is essentially homogeneous Form A crystal modification.

The Form A crystal modification of F-HCl is prepared in an environmentally friendly manner by crystallization from an aqueous solution of F-HCl at a temperature in the range from 5°C to 50°C, preferably in the range from 20°C to 40°C. Generally, a temperature of about 30°C is optimal. If the crystallization is carried out at the higher and lower temperatures in the above defined temperature ranges the resulting product can be a mixture of crystal forms which includes Form A.

Generally, crystalline or non-crystalline F-HCl is dissolved in water with stirring to form an aqueous solution of F-HCl. The temperature of the aqueous solution of F-HCl is then adjusted to the desired temperature range, for example, by placing it in a water or oil bath, the solution is stirred and the water allowed to partially evaporate to yield Form A crystals of F-HCl. Preferably, the evaporation of the water is assisted, for example, by passing a gentle stream of air over the surface of the solution or reducing the pressure above the solution. However, the solution should be maintained in the temperature ranges identified above while the water evaporates from the solution.

Advantageously, no co-solvent or additional organic material is present in the water used to prepare th aqueous solution. However, minor amounts of such co-solvents or additional organic materials are not known to cause any significant disadvantage.

Thus, the present invention relates to a method of preparing the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride, which comprises preparing an aqueous solution of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride; and crystallizing the α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride from the aqueous solution at a temperature of from 5°C to 50°C. Preferably, the crystallization is carried out at a temperature of 20°C to 40°C. Optimally, the crystallization is carried out at a temperature in the range from 25°C to 35°C, most optimally at about 30°C.

The crystallization step is effected by methods known in the art for precipitating a solute from solution, for example, by reducing the volume of solvent by evaporation or other means, or by addition of a co-solvent which induces crystallization and seeding.

Preferably, the crystallization step is effected by reducing the volume of water in the aqueous solution. Thus, the present invention further relates to a process wherein the crystallization step is effected by reducing the volume of water in the aqueous solution by an amount sufficient to promote crystallization. Preferably, the volume of water is reduced by evaporation of the water. This can be assisted by blowing a stream of air over the surface of the aqueous solution or by reducing the pressure above the solution in some other way.

The Form A crystal modification of F-HCl is used, in particular, for the preparation of pharmaceutical compositions of F-HCl. Thus, the present invention further relates to a pharmaceutical composition which comprises a pharmaceutically effective amount of the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride. Preferably, the pharmaceutically effective amount is the amount required to deliver 50 to 150 mg/day.

The following example is intended to illustrat , but not limit, the invention. All melting points are uncorrected unless otherwise noted.

Example 1

A 0.51 gram sample of F-HCl (melting point range from 192°C to 198°C) is dissolved in 100 mL of deionized water by heating on a water bath at 80°C and stirring at moderate speed with a 1 cm Teflon coated magnetic stirring bar. The temperature of the aqueous solution is reduced to 30°C and held at that temperature in the water bath as a gentle stream of air is passed over the surface. After about half of the water evaporates (approximately 7 hours), the crystalline precipitate of Form A F-HCl is separated by vacuum filtration with a Hirsch funnel. The sample is protected from dust by a filter paper cover and allowed to dry in the air for approximately 48 hours.

The Form A F-HCl thus prepared exhibits a melting point of 142°C to 145°C, determined in an open glass capillary suspended in circulating oil using a Thomas Hoover Melting Point Apparatus, the powder x-ray diffraction pattern is depicted in Figure 1 and Table 1, the solid state carbon-13 NMR spectrum depicted in Figure 2 and Table 2, and the FTIR spectrum depicted in Figure 3 as a Nujol mull.

We claim:

1. The compound α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from 138°C to 148°C.

2. The compound α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from about 142°C to about 145°C.

3. A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by powder x-ray diffraction peaks at d spacings of about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35.

4. The crystal modification of claim 3 having the powder x-ray diffraction pattern depicted in Figure 1.

5. The crystal modification of claim 3 characterized by a melting point in the range from about 142°C to about 145°C.

6. A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by solid state carbon-13 NMR signals at chemical shifts of about 187.4, 180.3, 74.5, 48.8, and 29.8 ppm.

7. The crystal modification of claim 6 having the solid state carbon-13 NMR spectrum depicted in Figure 2.

8. The crystal modification of claim 6 having powder x-ray diffraction peaks at d spacings of about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35.

9. The crystal modification of claim 8 having a melting point in the range from about 142°C to about 145°C.

10. Th crystal modification of claim 8 having a melting point in the range from about 138°C to 148°C.

11. Th crystal modification of claim 7 having the powder x-ray diffraction pattern depicted in Figure 1.

12. The crystal modification of claim 11 having the Fourier Transform Infrared Spectrum depicted in Figure 3 as a Nujol oil mull.

13. The crystal modification of claim 12 having a melting point in the range from about 138°C to about 148°C in substantially pure form.

14. The crystal modification of claim 13 having a melting point in the range from about 142°C to about 145°C in pure form.

15. The crystal modification of claim 14 in highly pure form.

16. A process for preparing the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride, which comprises

(a) preparing an aqueous solution of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride; and

(b) crystallizing the α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride from the aqueous solution at a temperature of from 5°C to 50°C.

17. A process of claim 16 wherein the temperature is in the range from 20°C to 40°C.

18. A process of claim 17 wherein the temperature is in the range from 25°C to 35°C.

19. A process of claim 18 wherein the temperature is about 30°C.

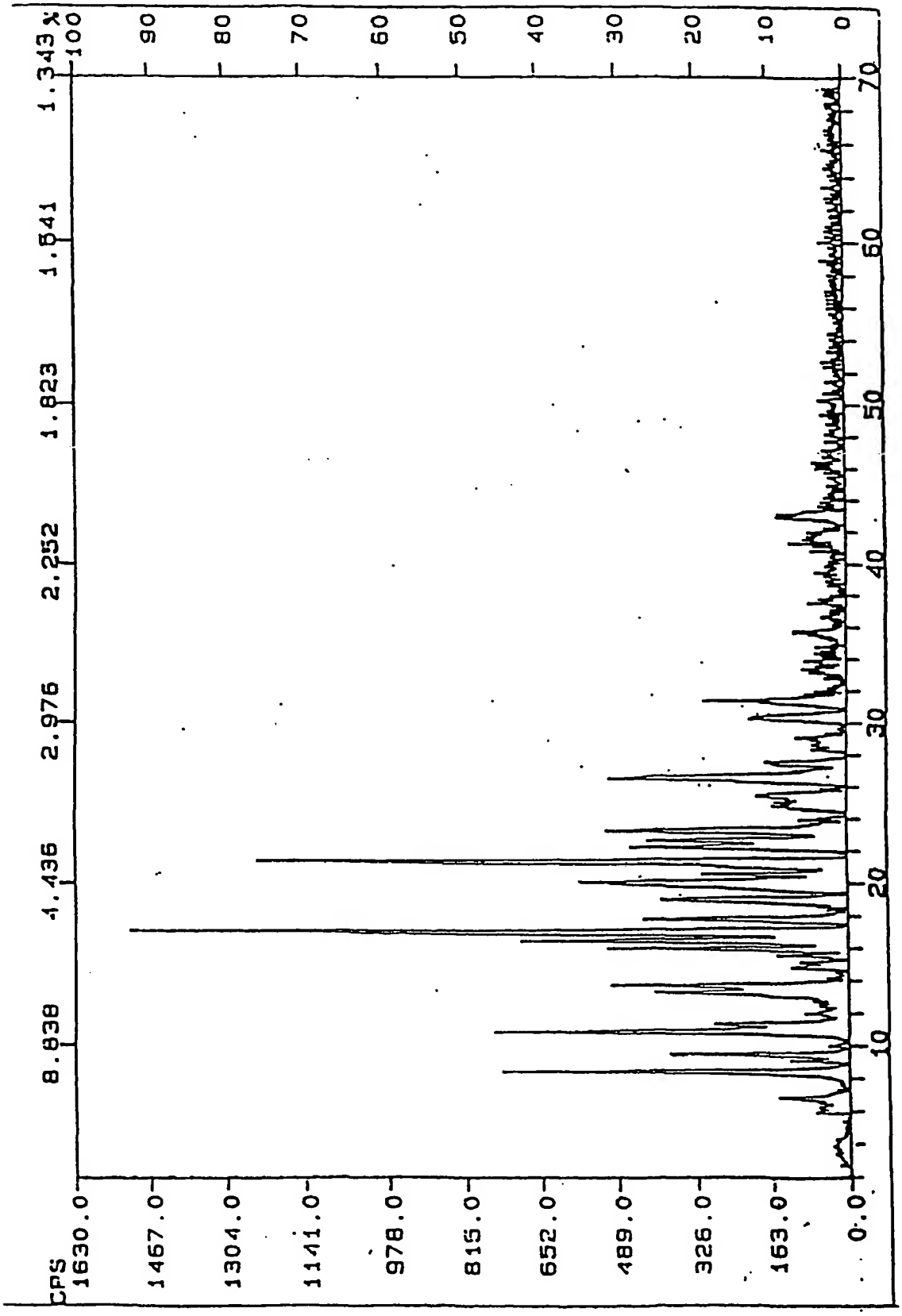
20. A process of claim 16 wherein the crystallization step is effected by reducing the volume of water in the aqueous solution by an amount sufficient to promote crystallization.

21. A process of claim 19 wherein the crystallization step is effected by reducing the volume of water in the aqueous solution by an amount sufficient to promote crystallization.

22. A process of claim 21 wherein the volume of water is reduced by evaporation.

23. A process of claim 16 wherein the α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride produced is pure Form A crystal modification.

FIGURE 1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10

FIGURE 2

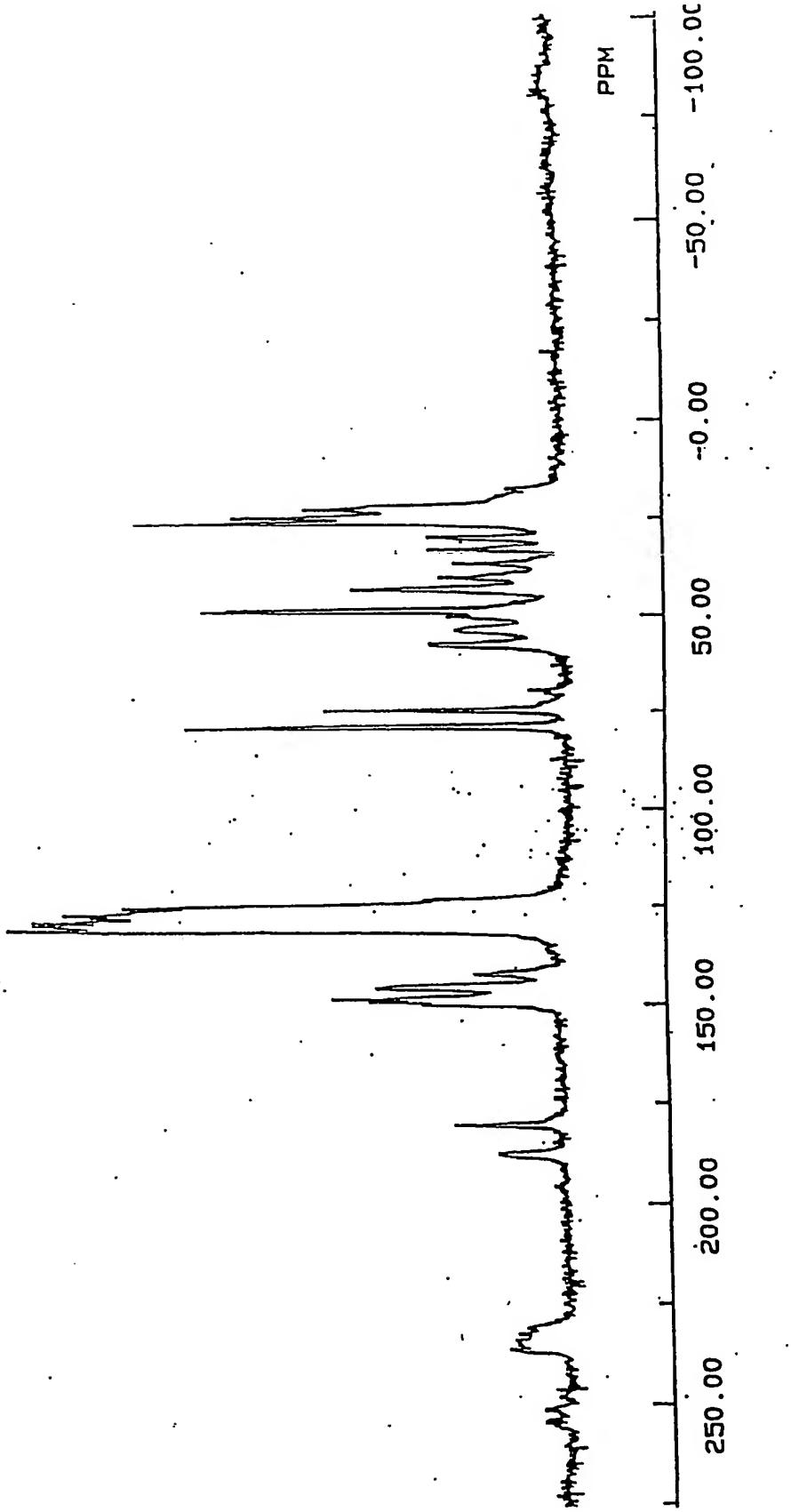


FIGURE 3

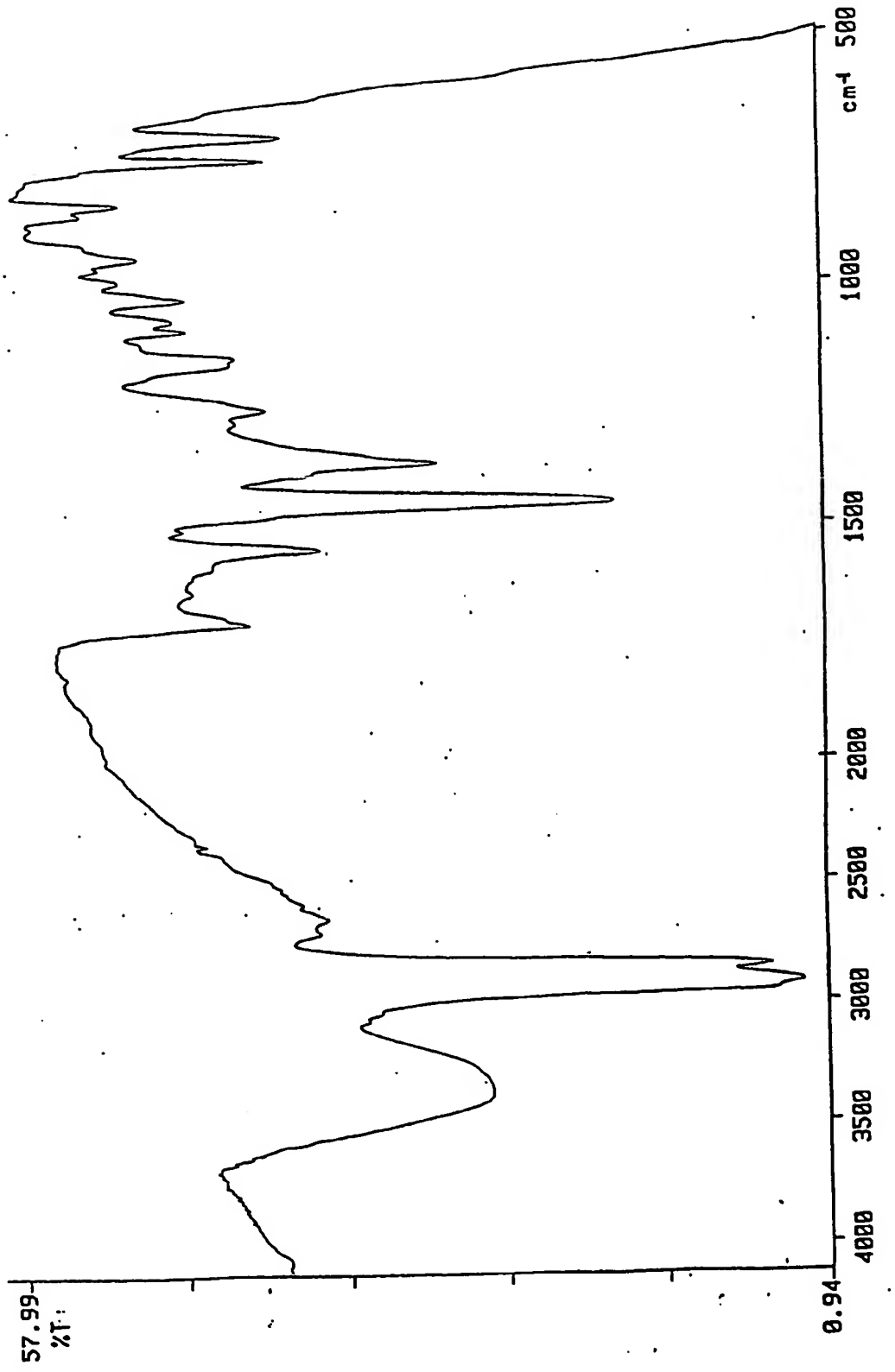
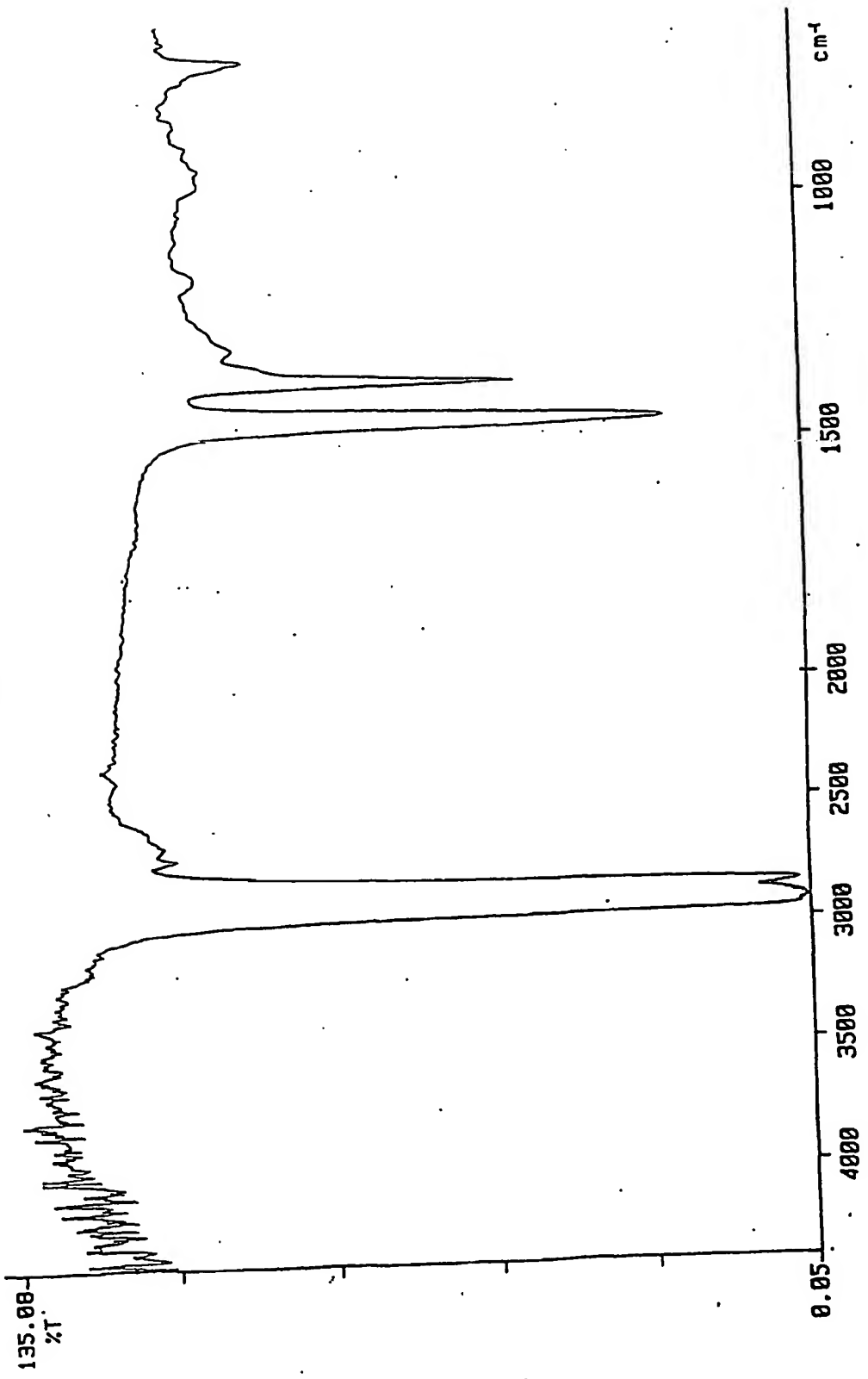


FIGURE 4



10/009230

8

PATENT COOPERATION TREATY

PCT

REC'D 05 APR 2002
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-159WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB00/00708	International filing date *(day/month/year)* 25 MAY 2000	Priority date *(day/month/year)* 25 MAY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): IPC7 A61K 31/445; C07D 211/22, 34 and US Cl.: 514/317; 546/239, 240		
Applicant RANBAXY LABORATORIES LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 NOVEMBER 2000	28 FEBRUARY 2002
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer CELIA CHANG
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB00/00708

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-7 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 8-9 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages 1-4 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB00/00708

V. Reasoned statement under Article 35(2) with regard t novelty, inventive step r industrial applicability; citati ns and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-13	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-13	NO
Industrial Applicability (IA)	Claims	1-13	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-13 meet the criteria set out in PCT Article 33(2) for novelty, because the prior art does not teach the specific amorphous form of fexofenadine.

Claims 1-13 lack an inventive step under PCT Article 33(3) as being obvious over Carr et al. US 4,254,129, column 13, example 3, or Carr et al. US 4,285,957 column 13, example 3 or Marion Derrel Dow, Inc. WO 95/31437 claims 10-11, 13-15, 17-19 in view of Lieberman, Suzuki, Corrigan CA 98, Nuernberg CA 86 and Sato et al. CA 110. The two Carr et al. references and the WO 95/31437 patent disclosed the claimed compound. The difference is that the particular amorphous form was not named. one having ordinary skill in the art would be motivated to make an amorphous form employing spray drying or freeze drying process because not only spray drying and freeze drying are size reduction routine formulation to enhance drug dissolution but also such processes would inherently produce the amorphous form in drugs with polymorphism. Please note that the specific solvent system are well recognized being choice of solvents which have fexofenadine solubility (see WO 95/31437 page 11 lines 22-29).

Claims 1-13 meet the criteria set out in PCT Article 33(4), because the prior art did not indicated the drug in its amorphous form would not be industrially applicable.

---------- NEW CITATIONS ----------

Database CAS on STN (COLUMBUS, oh, usa), Accession No. 110:179429, SATA et al. Physico-pharmaceutical studies on 9,3"-diacetylmidecamycin. Part 3. Amorphous formation of 9,3"-deactylmidecamycin by freeze drying and through grinding. YAKUZAIGAKU v.48 (4) pages 296-304 (1988).

INTERNATIONAL SEARCH REPORT

Internati nal application No.
PCT/IB00/00708

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/445; C07D 211/22, 34
US CL :514/317; 546/239, 240
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/317; 546/239, 240

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS--structure
EAST/WEST-- subclasses and image

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,254,129 A (CARR ET AL.) 03 March 1981, see entire document, especially column 13, example 3.	1-2
Y	US 4,285,957 A (CARR ET AL.) 25 August 1981, see entire document, especially column 13, example 3.	1-2
Y	WO 95/31437 A1 (MARION MERREL DOW INC.) 23 November 1995, see entire document, especially claims 10-11, 13-15, 17-19.	1-13
Y	LIEBERMAN, Herbert A. Pharmaceutical dosage forms. New York, Marcel Dekker, Inc., 1989, Volumn 2 page 463, see entire document.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
05 SEPTEMBER 2000

Date of mailing of the international search report
11 OCT 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
CELIA CHANG
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

Internati nal application No.
PCT/IB00/00708

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SUZUKI, E. et al. Studies on method of particle size ruduction of medicinal compounds. VIII.[1)] Size reduction by freeze-drying and the influence of pharmaceutical adjuvants on the micromeritic properties of freeze-dried powders. Chem. Pharm. Bull. 1979, Vol. 27, No. 5, pages 1214-1222, see entire article.	1-13
Y	Database CAS on STN (COLUMBUS, OH, USA) Accession No. 98:166814, CORRIGAN et al. Physicochemical properties of spray dried drugs: phenobarbitone and hydroflumethiazide. Abstract, Drug Dev. Ind. Pharm. 1983, Vol. 9, No. 1-2, pages 1-20, see entire article.	1-13
Y	Database CAS on STN (COLUMBUS, OH, USA) Accession No. 86:8603, NUERNBERG, E. Colloidal distribution states in pharmaceutical technology. Manufacture and qualities of pharmaceutical preparations by spray drying. Abstract, Prog. Colloid Polym. Sci. 1976, Vol. 59, pages 55-59, see entire article.	1-13

APR 0 2 2002

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: RAINBAXY LABORATORIES LIMITED
C/O DESHMUKH, JAYADEEP R.
600 COLLEGE ROAD EAST
SUITE 2100
PRINCETON, N.J. 08540

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	28 MAR 2002
Applicant's or agent's file reference: RLL-159WO	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/IB00/00708	25 MAY 2000	25 MAY 1999

Applicant
RANBAXY LABORATORIES LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

ENTERED

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer CELIA CHANG
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/416 (July 1992)★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-159WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB00/00708	International filing date *(day/month/year)* 25 MAY 2000	Priority date *(day/month/year)* 25 MAY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): IPC7 A61K 31/445; C07D 211/22, 34 and US Cl.: 514/317; 546/239, 240		
Applicant RANBAXY LABORATORIES LIMITED		

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   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 NOVEMBER 2000	28 FEBRUARY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CELIA CHANG Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB00/00708

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-7 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 8-9 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

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pages 1-4 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

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[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB00/00708

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-13	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-13	NO
Industrial Applicability (IA)	Claims	1-13	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-13 meet the criteria set out in PCT Article 33(2) for novelty, because the prior art does not teach the specific amorphous form of fexofenadine.

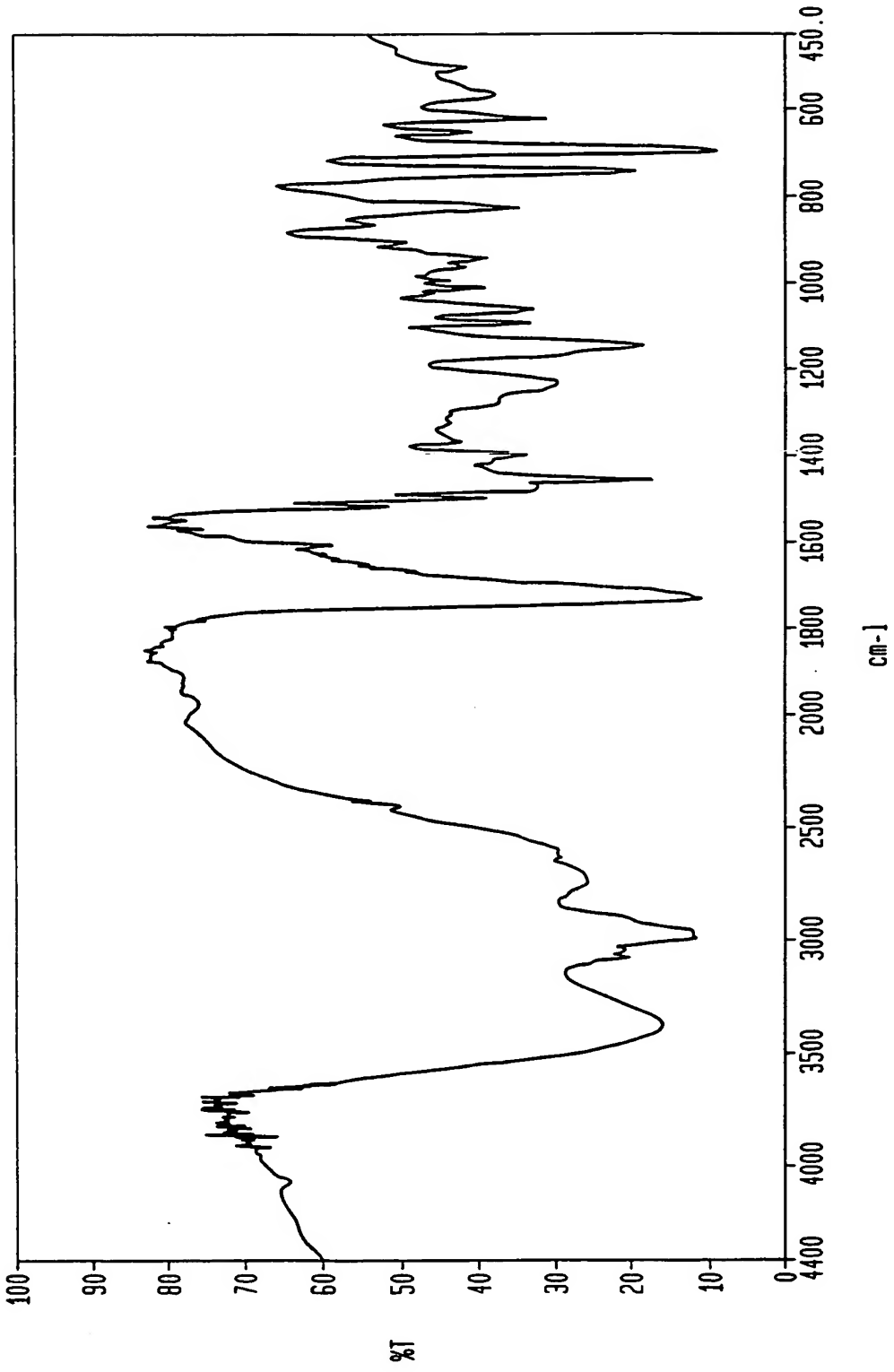
Claims 1-13 lack an inventive step under PCT Article 33(3) as being obvious over Carr et al. US 4,254,129, column 13, example 3, or Carr et al. US 4,285,957 column 13, example 3 or Marion Derrel Dow, Inc. WO 95/31437 claims 10-11, 13-15, 17-19 in view of Lieberman, Suzuki, Corrigan CA 98, Nuernberg CA 86 and Sato et al. CA 110. The two Carr et al. references and the WO 95/31437 patent disclosed the claimed compound. The difference is that the particular amorphous form was not named. one having ordinary skill in the art would be motivated to make an amorphous form employing spray drying or freeze drying process because not only spray drying and freeze drying are size reduction routine formulation to enhance drug dissolution but also such processes would inherently produce the amorphous form in drugs with polymorphism. Please note that the specific solvent system are well recognized being choice of solvents which have fexofenadine solubility (see WO 95/31437 page 11 lines 22-29).

Claims 1-13 meet the criteria set out in PCT Article 33(4), because the prior art did not indicated the drug in its amorphous form would not be industrially applicable.

---------- NEW CITATIONS ----------

Database CAS on STN (COLUMBUS, oh, usa), Accession No. 110:179429, SATA et al. Physico-pharmaceutical studies on 9,3"-diacetylmidecamycin. Part 3. Amorphous formation of 9,3"-deactylmidecamycin by freeze drying and through grinding. YAKUZAIGAKU v.48 (4) pages 296-304 (1988).

FIG. 1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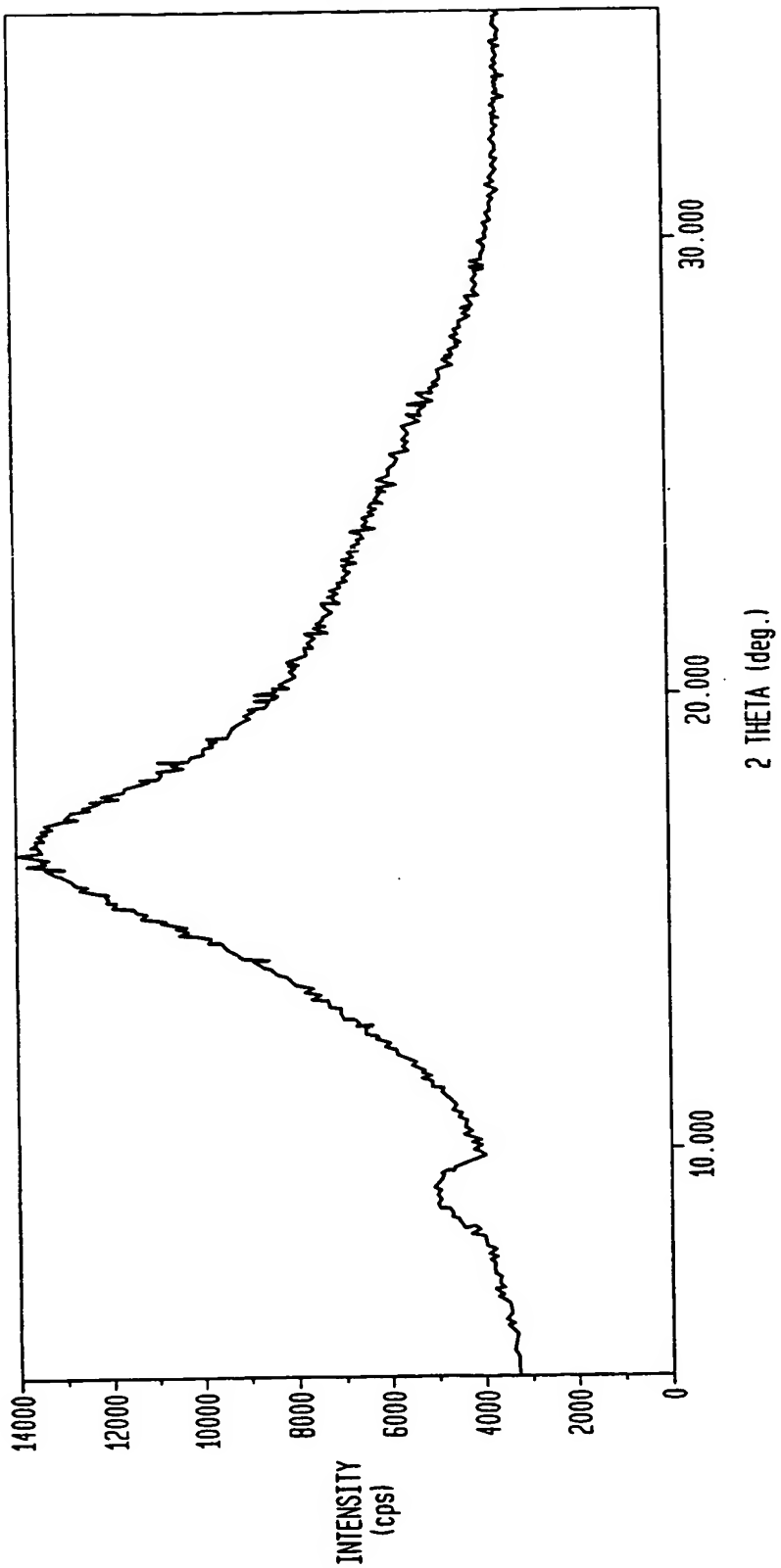
cm-1

FIG. 2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20.000
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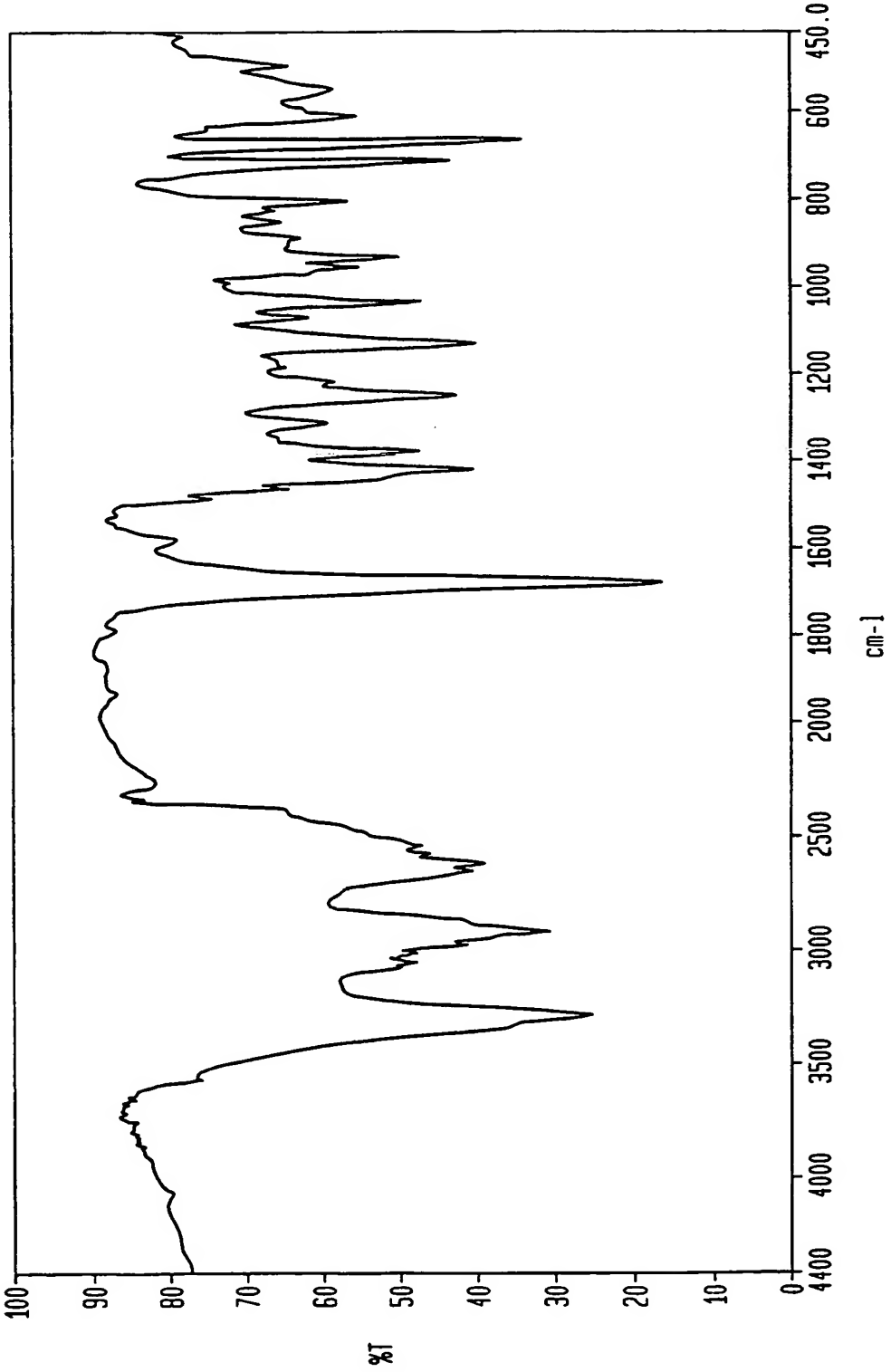
FIG. 3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0
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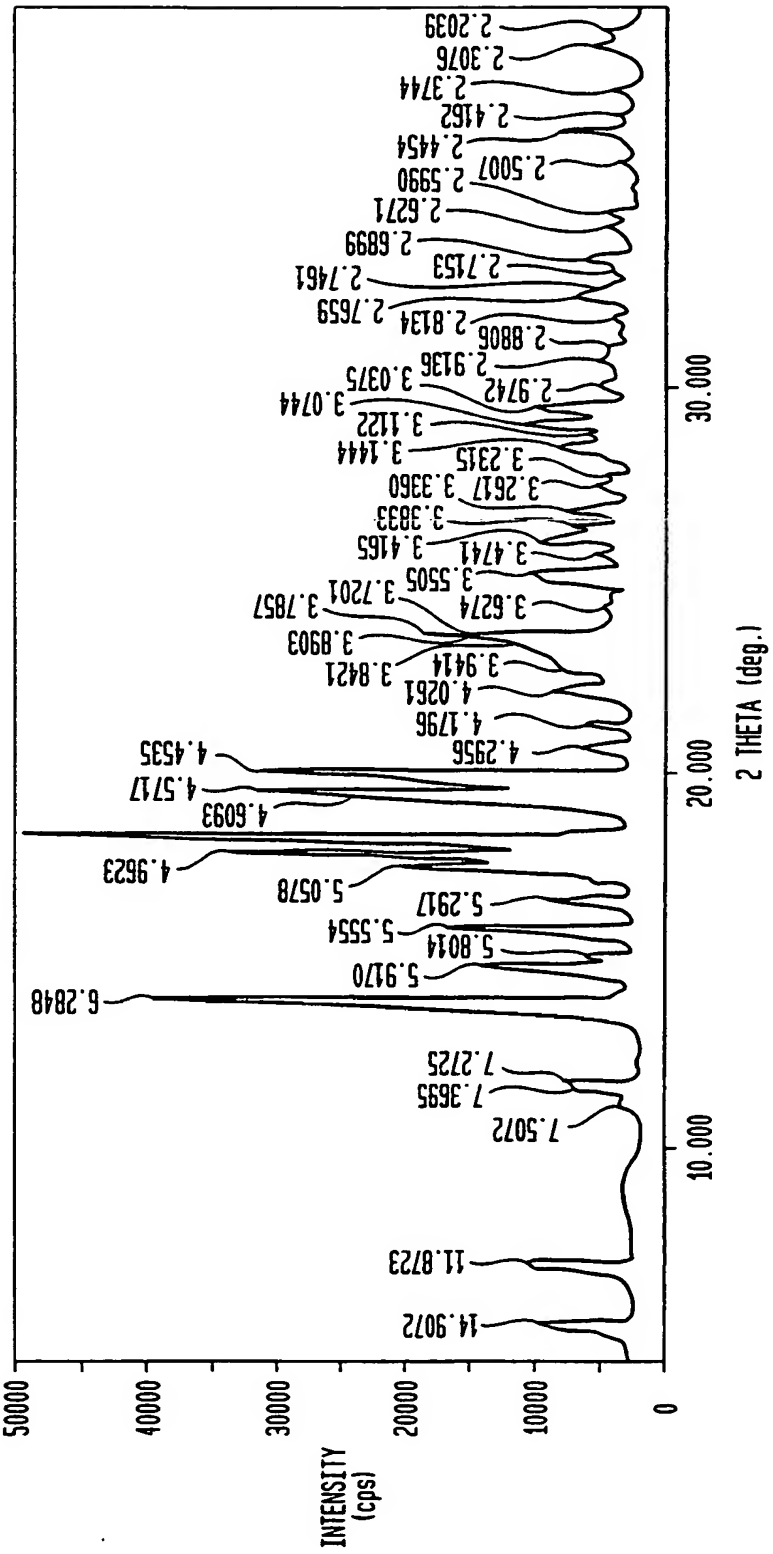
cm-1

FIG. 4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20000
10000
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20.000
30.000
2 THETA (deg.)